

REMARKS

Claims 17 and 83 remain in this case, and were finally rejected in the previous Office Action, issued July 20, 2007. New claims 95 and 96 are added. In view of the arguments and remarks set forth below, Applicant's respectfully request reconsideration.

New Claim

Claim 95 and 96 are added, describing the XRD diffractogram shown in Fig. 2 of the application. Support for this claim is found on page 18, lines 19-22.

Claim Rejection Under 35 U.S.C. §102/103

Legal Section

According to MPEP 2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

The determination of obviousness under 35 U.S.C. § 103(a) is based upon the factual inquiries set forth by the U.S. Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 17-18. These factual inquiries are: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims in issue; resolving the level of ordinary skill in the pertinent art; and evaluating evidence of secondary considerations. *Id.* In formulating an obviousness rejection based upon a combination of prior art elements, it is necessary for the Office to identify a reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. When performing this analysis,

[I]t will often be necessary to look to interrelated teachings of multiple patents; to the effect of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___, 127 S. Ct. 1727, 1740-41 (2007).

Argument

Claims 17 and 83 now stand rejected under 35 U.S.C. §102(b) and 103 over Buhlmayer et al, in US 5,399,578. The Examiner is of the view that Buhlmayer's product inherently anticipates the instant invention of pure amorphous valsartan. Applicants respectfully traverse this rejection.

The attached declaration of Dr. Valerie Niddam-Hildesheim, describes the isolation of valsartan from ethyl acetate, as was disclosed in Buhlmayer example 16. The two batches in which this done, designated samples A and B, yielded similar PXRD patterns, indicating that the material obtained from ethyl acetate was not purely amorphous. The analysis and discussion of the PXRD appears in the attached declaration of Dr. Tamás Koltai. The PXRD patterns contain distinct maxima about 6, 14, and 23° 2θ. By contrast, pure amorphous material prepared in accordance with the instant invention is a smooth halo. See Figure 2 of the instant invention. Note also that the PXRD diffractograms of valsartan "from ethyl acetate" in the declaration are very similar in appearance to the "valsartan essentially amorphous" material, illustrated in Figure 24 of the instant application. In Dr. Koltai's opinion, the valsartan obtained from ethyl acetate is not pure amorphous, but rather shows significant crystalline impurities, as shown by the features in the PXRD diffractogram and the large melting enthalpy.

The instant claims recite amorphous valsartan in a highly pure form, which is characterized by the absence of a peak in DSC and the absence of peaks in XRD. This level of purity of the amorphous was not previously reported, nor suggested, in Buhlmayer or in Marti, et al. in WO 02/06253. Buhlmayer did not discuss polymorphism at all, and the

discussion of the "almost amorphous" valsartan in the Marti publication appears to be merely a discussion of the prior art in Buhlmayer, and not part of the alleged inventions in Marti.

Valsartan is also disclosed in Buhlmayer in example 37, where it was stated that recrystallization from diisopropyl ether afforded valsartan melting at 116-117 °C. Col. 43, ll. 8-9. Dr. Koltai states that the sharp melting point from example 37 is indicative of crystalline material.

"The process of crystallization is affected by many physical parameters. . . this element of unpredictability has serious implications for solids design in crystal engineering." M. Caira, "Crystalline Polymorphism of Organic Compounds," Topics in Current Chemistry, vol. 198, 164-208 (1998) at 164. Buhlmayer and/or the Marti publication do not render the present claims obvious because there is no teaching or suggestion in Buhlmayer or Marti to prepare highly pure amorphous valsartan, particularly in light of unpredictable nature of polymorphism.

In the July 20, 2007 Office Action, the Examiner states that:

RECOGNIZED AT THE TIME OF THE INVENTION. MPEP 2112. Applicants state that "the fact that Bulmayer provides a melting range for its product means that its product is not purely amorphous" on page 7 of the response. This statement is unclear because in Claim 83 there is a melting point range. Please see discussion of melting points and other characteristics in the previous office action.

Claim 83 provides a region of temperature in a DSC analysis, in which there is no melting enthalpy above 1 J/g is in the region of about 80° C to about 100° C. This is not a melting point range, but rather a range of temperatures in the DSC analysis where the curve is particularly straight, which is indicative of a lack of a melting enthalpy.

The Applicants have added to new claims directed to XRD patterns of the product. The attached declarations clearly show that the product of Buhlmayer lacks the XRD pattern claimed in claims 95 and 96.

CONCLUSION

Accordingly, the Applicants submit that the concerns of the Examiner have been fully addressed, and that the current claims are patentable over the prior art and in condition for allowance. The Examiner is invited to contact the undersigned at 212-908-6257 to discuss any remaining issues prior to the issuance of a further Office Action.

Respectfully submitted,

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